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Dated: 6/15/04Signature: [Signature]

(Ginny Blundell)

Docket No.: VASG-P03-003  
(PATENT)**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**In re Application of:  
Gill et al

Application No.: 09/805,761

Group Art Unit: 1635

Filed: March 13, 2001

Examiner: McGarry, S.

For: METHOD AND COMPOSITIONS FOR  
ANTISENSE VEGF OLIGONUCLEOTIDESMail Stop AF  
Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450**DECLARATION UNDER 35 U.S.C. §1.132 OF PARKASH GILL**

Sir:

DR. PARKASH GILL hereby declares and states as follows:

1. I am a named inventor of the above-identified patent application, and the subject matter described and claimed therein.
2. I am Professor of Medicine and Pathology at the Keck School of Medicine at the University of Southern California. I have worked on the development of clinically useful antisense nucleic acids for over 10 years. A copy of my CV is enclosed with this Declaration.
3. **The Office Action:** I have read the Office Action issued by the U.S. Patent and Trademark Office on December 15, 2003 in the above-identified patent application. I have also reviewed the references cited in the Office Action, including Uchida et al., U.S. Patent No. 6,150,092. I understand that the Examiner has rejected the pending claims as obvious in view of Uchida et al. in combination with various other references. From a scientific perspective, I do

not believe that the Uchida et al. reference renders the claims of the present application obvious. Had I read the Uchida et al. reference at the time that the present application was filed, January 19, 2000, I would not have been motivated to generate 2'O-methyl- modified forms of any of the VEGF antisense nucleic acids set forth in Uchida et al. In addition, I would not have been motivated to generate VEGF antisense nucleic acids having both 2'O-methyl and phosphorothioate modifications. I base this conclusion on reasons set forth below.

4. **2'O-methyl and Phosphorothioate-modified antisense probes:** First, I note that PS- and 2'O-methyl-modified antisense probes are designed for use in *in vivo* or cell-based applications of antisense technology. This is because PS- modified or 2'O-methyl-modified nucleic acids have improved resistance to nucleases found in cells. 2'O-methyl-modified nucleic acids are also particularly useful for oral administration. One would have no reason to make a PS- or 2'O-methyl-modified form of an antisense nucleic acid unless one intended to use the antisense construct to affect gene expression in cells. Therefore, a demonstration that an unmodified antisense probe is effective in a cell-free assay would not necessarily provoke one to make and test the modified form (e.g., PS-modified and/or 2'O-methyl-modified) in a cell-based assay. This is particularly true where, as with Uchida et al., there is a poor correlation between the results seen in the cell-free and cell-based assays.

5. **Cell-free Assays:** Uchida et al. describe experiments testing antisense probes for their effects on VEGF expression. The majority of the data presented by Uchida et al. were based on cell-free assays employing unmodified DNA antisense probes at a concentration of 0.4 micromolar (see, Tables 1-8 of Uchida et al. and col. 20, line 3). Tables 1 and 2 in particular show that dozens of unmodified antisense probes were effective in decreasing VEGF expression in the cell-free assay. In many instances VEGF expression was decreased by greater than 90%.

6. **Cell-based Assays:** Uchida et al. selected six probes that were highly effective in the cell-free assays and tested PS-modified forms of these probes in a cell-based assay. The effects of these probes on VEGF expression in cells are shown in Table 9. The amount of VEGF expression observed by Uchida et al. in the presence of the PS-modified probes was high, ranging from 54% to 70% of normal (59% to 82% when corrected for the baseline inhibition

seen in the controls). Uchida et al. do not provide any description with respect to 2'O-methyl-modified probes.

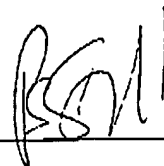
The cell-based assays of Uchida et al. were performed with PS-modified probes at the high concentration of 20 micromolar (Col. 25, line 30). In contrast, the cell-free assays in Tables 1 and 2 were performed at a concentration of 0.4 micromolar. At a concentration of 20 micromolar, it is often difficult to discern whether an effect on gene expression is due to a specific antisense effect or a generalized effect on cellular processes. Given the high probe concentration and the small observed effect on VEGF expression in the cell-based assays, I conclude that the antisense probes identified by Uchida et al. are not effective for inhibiting VEGF expression in cells. These data would not have motivated me to modify and test other probes disclosed by Uchida et al. for use in cells.

7. **A Comparison of the Cell-free and Cell-based Assays:** There is a poor correlation between the effectiveness of the unmodified probes in the cell-free assays and the PS-modified probes in the cell-based assays. For example, the unmodified probe A311 (SEQ ID NO: 51) of Uchida et al. inhibited 96% of VEGF expression in the cell-free assay, but the PS-modified form of A311 inhibited only 22% to 28% of VEGF expression in the cell-based assay (at a 50-fold higher concentration). Of six probes that were effective in cell-free assays, all six showed only mild effect on VEGF expression in the cell-based assay. I conclude that there is no reason to expect that any of the probes that Uchida et al. identified in the cell-free assay would be likely to be effective as PS-modified forms.

8. I further state that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June 14, 2004

Signed: \_\_\_\_\_



Dr. Parkash Gill